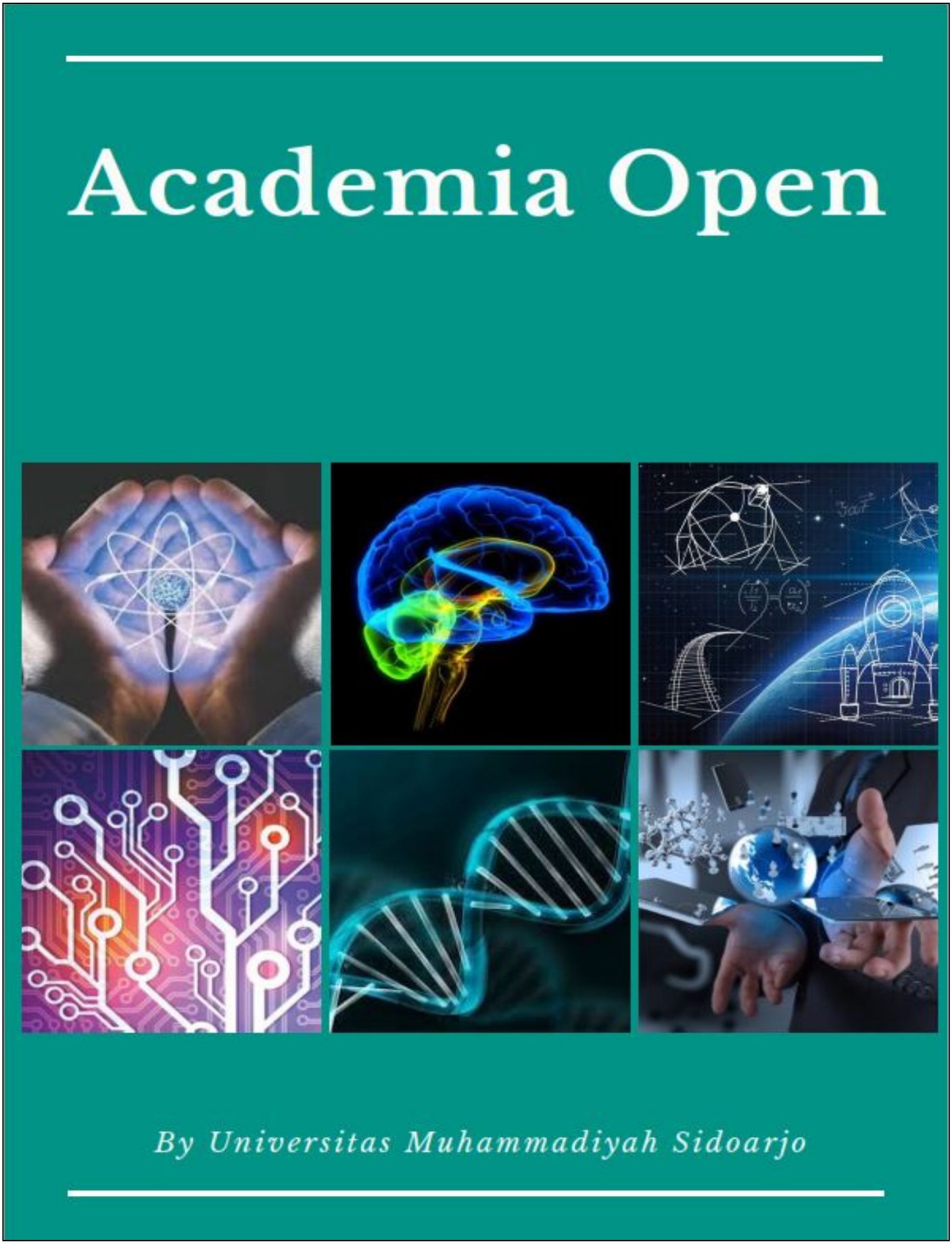
Academia Open
Vol 9 No 1 (2024): June
DOI: 10.21070/acopen.9.2024.8793 . Article type: (Medicine)

Table Of Content

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 9 No 1 (2024): June
DOI: 10.21070/acopen.9.2024.8793 . Article type: (Medicine)



ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 9 No 1 (2024): June
DOI: 10.21070/acopen.9.2024.8793 . Article type: (Medicine)

Originality Statement

The author[s] declare that this article is their own work and to the best of their knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the published of any other published materials, except where due acknowledgement is made in the article. Any contribution made to the research by others, with whom author[s] have work, is explicitly acknowledged in the article.

Conflict of Interest Statement

The author[s] declare that this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright Statement

Academia Open
Vol 9 No 1 (2024): June
DOI: 10.21070/acopen.9.2024.8793 . Article type: (Medicine)

EDITORIAL TEAM

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 9 No 1 (2024): June
DOI: 10.21070/acopen.9.2024.8793 . Article type: (Medicine)

Article information

Check this article update (crossmark)

Check this article impact (*)

Save this article to Mendeley

(*) Time for indexing process is various, depends on indexing database platform

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 9 No 1 (2024): June
DOI: 10.21070/acopen.9.2024.8793 . Article type: (Medicine)

Preeclampsia Management: Advancements, Guidelines, and Emerging Perspectives

Manajemen Preeklampsia: Kemajuan, Pedoman, dan Perspektif yang Muncul

Zainab Abdlkadhim Aboshnin, zainab.abdlkadhim@mu.edu.iq, (1)
Department of Pharmacology, Al-Muthanna University, Iraq

Safa Azhar Razzaq, safa_azhar@mu.edu.iq, (0)
Department of Pharmacology, Al-Muthanna University, Iraq

Layla Hammody Hashem, Layla.alobaid@mu.edu.iq, (0)
Department of Pharmacology, Al-Muthanna University, Iraq

(1) Corresponding author

Abstract

Chronic elevation in blood pressure during gestation poses a significant risk for maternal mortality, particularly in the United States. Understanding the pathophysiology of preeclampsia, a specific form of gestational hypertension, has led to developments in management strategies aimed at improving outcomes for both mothers and babies. This abstract outlines the underlying mechanisms, international guideline-based management approaches, and newer perspectives in addressing hypertension during pregnancy. The goal is to balance risks and benefits effectively, enhancing the care of pregnant women with hypertension.

Highlights:

- Understanding the pathophysiology of preeclampsia is crucial for effective management.
- International guidelines provide a framework for optimizing care for pregnant women with hypertension.
- Emerging perspectives offer insights into potential advancements in treatment strategies.

Keywords: Hypertension, Preeclampsia, Eclampsia, Antihypertensive Drugs

Published date: 2024-06-01 00:00:00

Academia Open
Vol 9 No 1 (2024): June
DOI: 10.21070/acopen.9.2024.8793 . Article type: (Medicine)

Introduction

Hypertensive disorders of pregnant women considered as the main cause of maternal and fetal morbidity and mortality. Hypertension disorder in pregnancy can be define in the presence of a systolic blood pressure (SBP) 140 mmHg and/or diastolic blood pressure (DBP) 90 mmHg however chronic elevation in blood pressure also could be classified as mild, moderate or severe depend on the level of blood pressure as following :

1. Mild Hypertension: Diastolic blood pressure 90–99mmHg, systolic blood pressure 140– 149mmHg.

2. Moderate Hypertension: Diastolic blood pressure 100–109mmHg, systolic blood pressure 150–159mmHg.

3. Severe Hypertension: Diastolic blood pressure 110mmHg or greater, systolic blood pressure 160mmHg or greater.

Pregnant with hypertension can developed range of serious complication, one of most deleterious of this complication is preeclampsia, specific type of hypertension occur during pregnancy that attributed to either worsening in chronic hypertension or de novo occurring [1]. The definition of Preeclampsia disorder based on presence of hypertension (≥140/90 mm Hg) and proteinuria (≥300 mg in a 24-hour urine), this condition affects 3–4% of all pregnancies in the world. In recent procedure of preeclampsia diagnosis , that detection of proteinuria should not be mandatory to conform the diagnosis because many cases of preeclampsia appear as non-proteinuria condition which suggesting that a subclass of “non-proteinuria preeclampsia” should be recognized[2] [3].

The incidence of preeclampsia increased in the presence of one or more of these conditions include previous preeclampsia, ethnicity (black women are more at risk), multiple gestations, increased maternal body mass index before pregnancy, and comorbid medical disorders such as kidney diseases and diabetes mellitus [4]. This maternal disorder showed involvement many systems dysfunction such as cardiac, vascular, placental, and immunological system. Initially the preeclampsia associated with partial dysfunction in placental angiogenesis combined with triggered the inflammatory response. All these events developed fetal complication showed as premature delivery, growth retardation, and death, Therefore the proper management is necessary to reduce and prevent maternal and fetal complication[5].

Method

The information and fact presented in this review depended on previous searches and articles. The work utilized studies on chronic hypertension, preeclampsia, eclampsia, the current guidelines of management for pregnant women with hypertension, and the mechanism of action for the antihypertensive agent that was previously and recently used for controlling gestational hypertension. The search was carried out on September 25, 2023, in Google Scholar, Medline Ovid, PubMed, and Web of Science. The selection of studies was performed by pairs of researchers (ZA,SA) independently; however, LH was referred to as a third author in cases of disagreement.

Result and Discussion

A. Result

a. Pathophysiology

Preeclampsia can result from pregnancy with related hypertension disorder. The percent of occurrence of preeclampsia in general pregnant population estimated as 35% .The previous studies suggested the underlying mechanism of preeclampsia is the reduction of placental blood flow that trigger endothelial dysfunction in systemic vessels[6] which lead to tissue hypoxia due to reduction of oxygen supply that induced series of reaction including stimulate inflammatory response, imbalance of angiogenic and growth factors, aggregation of platelets which collectively lead to malfunction of endothelial system that appear clinically as preeclampsia[7].

The reduction in the level of vascular endothelial growth factor and placental growth factor together and elevated the level of these factors antagonist, the most abundant is the placental soluble fms-like tyrosine kinase1[8]. Placental ischemia can occur due to the reduction in the level of nitric oxide, the latter effect can attributed to action produced by the binding of vascular endothelial growth factor and placental growth factor to its receptors which in turn reduced the synthesis rate of nitric oxide, this mediator involved in many of vital processes that maintain the integrity of vascular endothelium[9].

After the delivery, about 27.5% of female could complained from de novo hypertension attributed to many factor such as administration of vasoactive drugs and fluid therapy or any agent or condition lead to flow of fluid from interstitial to intravascular space and finally rises the cardiac output all this factors trigger the compensatory

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

responses of general vasodilation and increases urine out put that end with increases the measurement of blood pressure[10].

b. Classification

Gestational hypertension categorized to three main types depended on the onset time of hypertension in pregnant female and the associated complication [11]:

1. Pre-Existing Hypertension (Persistent Hypertension of All Causes)

Pre-existing hypertension is referred to chronic elevation of blood pressure that developed before the conception or that arises below twenty weeks of conception. The frequency of this specific category is higher in developed population due to the older age of female at conception time and increased the incidence of fatness. Based on underlying causes of chronic hypertension can described into essential and secondary hypertension [12]. The clinical picture of preexisting hypertension appeared in two form; either combined with other comorbid condition such as renal disease or diabetes mellitus, this form necessitate more tight control for level of blood pressure prior to conception in order to protect the women from cardiovascular complication.

The second form is superimposed preeclampsia or with preeclampsia evidence, its diagnosis confirmed when the female with proteinuria or persistent hypertension showed on or more of the following criteria beyond the twenty weeks of gestation. This systemic criteria could be one or more of preeclampsia feature that involving new recent or worsening preexisting proteinuria, resistant hypertension and any of preeclampsia complication[13].

2. Non-Proteinuria Hypertension (Gestational Hypertension)

This condition characterized by the elevation of blood pressure measurements which occur for the first time at or more than 20 weeks of gestation, however the affected women with this type of hypertension may return to normal state within 3 months after birth date if the gestational hypertension recognized initially without any preeclampsia symptoms in the mother or fetus[14]. The chance that a woman with gestational hypertension would progress to developed preeclampsia or a poor pregnancy outcome increases when women affected with hypertension in early time of pregnancy and with more severe hypertension. A about 35% chance of preeclampsia is linked to gestational hypertension at less than 34weeks[15].

3. Preeclampsia

After twenty weeks of gestation, the new episode of elevated blood pressure (>140/90 mmHg) accompanied by substantial proteinuria (300mg/24 hour) referred as preeclampsia [16]. The latter state consider mild until diastolic or systolic levels reach or above 110 and 160 mmHg, respectively. It is suggested that a minimum of two blood pressure measurements made at least four hours apart be necessary for confirmed the diagnosis. The diagnosis of proteinuria confirmed when the 24 hour excretion of urine protein reaches or exceeds 300mg in day, or when the urinary protein\ creatinine ratio surpasses 0.3 mg\dL in single void urine sample [17].

c. Sign and Symptoms of Preeclampsia:

The condition may appear without any symptoms so the regular monitoring of blood pressure is very important to protect the mother and fetus safely. The symptoms of preeclampsia is largely dependent on the elevation blood pressure measurements which is may developed either suddenly or gradually. As mention previously the initial sign of this disorder is elevated blood pressure that beyond 140/90 mmHg documented on to reading, at least 4 hours apart [18].Other sign and symptoms may involve in women affected with preeclampsia showed as the following

1. Moderate to severe headache, anxiety,

2. Visual abnormalities, sensitivity to light, blurred vision.

3. Proteinuria, decreased total urine out-put

4. Gastrointestinal symptoms such as nausea, vomiting, abdominal pain.

5. Generalized edema, increased body weight

6. Liver function change.

In recent protocol of diagnosis which recommended via the International Society of Study of Hypertension in pregnancy confirmed the diagnosis regardless the absence of biochemical finding of proteinuria if specific finding are found together with recent onset of blood pressure elevation. There is specific type of preeclampsia which referred as HELLP syndrome that affected about 5% of cases and may quickly progress to condition consider as life threating state, this condition associated with hemolysis, decreased count of platelet, and aberrant rise of hepatic enzymes[19]. Eclampsia is another complication during the pregnancy period which known as the presence of

seizure in preeclampsia cases[20].

The diagnostic features of patients with preeclampsia could be grouped in Table 1 as following:

Diagnostic Feature	Description
Elevation of blood pressure	More than or equivalent to 140\90mmHg for systolic and diastolic measurement respectively, this reading beyond 20 weeks within pregnancy period in female with normal blood pressure reading before the gestation. While in female already diagnosed with chronic hypertension, the diagnosis of preeclampsia depended on elevation more than or equal to 160\110 mmHg for systolic and diastolic measurement respectively, in both states we need to reading separated by 4 hours.
Proteinuria	More than or equivalent to 300mg / 24 h in urine collection sample, protein on creatinine ratio more than or equal to 0.3, or the condition (preeclampsia) may occur in absence of proteinuria but the recent onset of hypertension accompanied with any of these condition below:
Low platelet count	platelet count below 100000\microliter.
Abnormal Kidney functions	Concentration of serum creatinine more than 1.1 mg\dL or twice fold than normal in case of absent other renal dysfunction, pulmonary or generalized edema.
Inadequate liver function.	Liver transaminases enzymes rises to about twice above the normal concentration.

Table 1. *Diagnostic Features of Patients with Preeclampsia*

d. Physiological Aspect of Proteinuria Throughout the Gestation

Throughout the normal gestational period there are physiological rise in the renal blood flow and glomerular filtration rate these change consider the main cause non pathological proteinuria that occur during pregnancy that range from 0.15 g\d before the conception to 3g\d during the trimesters, however all this events go away after the delivery[21]. Both glomerular and tubular type of proteins are involved in proteinuria, different proteins recognized but the most prevalent is Tamm-Horsfall protein which is derived from the renal tubules. Additional proteins include α1-antitrypsin, albumin, tranferrin, immunoglobulins, and low molecular weight protein. On the other hand preeclampsia definition involved the significant proteinuria which known globally as the excretion of protein in 24 hour urine collection greater than 300 mg[22].

The samples of urine used in proteinuria measurements needs to be as fresh as feasible. The chance of bacterial contamination increases directly with the length of time between the start of sample collection and test procedure and this lead to alteration or false results. Samples taken from patient must be use without refrigeration to sure that the results not affected also[23].

e. Drugs Used for Management Gestational Hypertension

The National High Blood Pressure Education Program's recommended slow release nifedipine, beta blockers (except atenolol), methyldopa, and diuretic agents as appropriate choice for treatment cases with preexisting hypertension[24].The hypertensive women may continue administering the same therapeutic agents prior to become pregnant with important note including the contraindication of angiotensin converting enzyme inhibitors such as captopril and angiotensinII receptor blocker such as valsartan due to teratogensity during the pregnancy so not used for such cases, While the in emergency treatment of preeclampsia the following agents labetalol, I.V hydralazine, and nifedipine consider the drug of choice[25].

f. Description of Recommended Drugs Used for Hypertension

The principles classes of the therapeutic agents which used for hypertension treatment rely on their mechanism of action. To show their pharmacological properties the following discussion explained the major six groups of antihypertensive agents:

1. Alpha2 Adrenergic Agonists (Methyldopa – Clonidine)

The two agents are centrally acting alpha2 adrenergic agonists (methyldopa acting centrally only while clonidine has central and peripheral action); however, its action deepened on the inhibitory mechanism for the sympathetic out flow which lead to reduction in level of catecholamine, vasodilation, reduced the total resistance of vascular

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

system with net result decrease in blood pressure[26]. Both agents taken orally with tolerable side effects although the methyldopa may increase the risk of depression so the caution should be taken in women with depressive disorders[27], also may cause change in sleep pattern and fatigue. Food and Drug Administration classified clonidine as category C while methyldopa category B in all trimesters without adverse effect on uteroplacental circulation or fetal growth[28].

2. Adrenergic Receptor Antagonists With Peripheral Action

This group including labetalol(mixed alpha and beta receptor antagonists) and prazosin (selective α1 antagoinst).Labetalol consider as nonselective beta blocker in addition to its action on alpha receptor that give the drug antihypertensive effect[29]. Due to the serious adverse effect of other beta blocker like atenolol which cause fetal growth restriction and decrease the weight of placenta its used not recommended normally ,These harmful action seen in pregnant women in second trimester used atenolol but not labetalol. However, the teratogenic effect of beta blocker is not established in pregnancy. The general side effects of this group which include sleep disturbance, fatigue, bronchoconstriction, and lethargy, also reported. Labetalol classified as category C and its use accompanied with elevated the risk of bradycardia and hypoglycemia in the newborn baby[30].

The action of prazocin on alpha1 receptors produced lowering in peripheral resistance which eventually decreasing the level of blood pressure. Postural hypotension and increase the heart rhythm consider the most common adverse effect and its use limited to some cases of chronic kidney disease in pregnant women[31].

3. Diuretics

This group contain several subclasses each one have mechanism and specific site of action in renal system, generally the benefits of diuretics in gestational hypertension restricted by the action of these agents on plasma volume that produced hypovolemia which in turn trigger the secretion of renin, angiotensin, and aldosterone, these event may exacerbated the hypertensive state[32]. Thiazides has category B according FDA classification so its use in pregnant women recommended in small doses to minimize its adverse effects on electrolyte balance and plasma volume[33].

4. Calcium Channel Blockers (Dihydropyridine and Non-D ihydropyridine)

Antihypertensive effect of both classes (Dihydropyridine and Non-dihydropyridine) attributed to its ability to inhibit the entry of calcium ions through calcium channel located in vascular smooth muscle[34]. Nifedipine (dihydropyridine) and verapamil(non-dihydropyridine) both agents classified via FDA as class C and not teratogenic drugs so consider as second choice for gestational hypertension. Generally all drugs in this group can cause maternal adverse effect including; tachycardia, facial flushing, headaches, and peripheral edema which related to vasodilator action of calcium channel blockers[35].

5. Intravenous Vasodilators

Hydralazine is intravenously used direct vasodilator used in case of sever gestational hypertension, some report consider hydralazine as second line after intravenous labetalol or the oral dosage form of nifedipine which is prescribed as first line in case of sever gestational hypertension, however FDA categorize hydralazine as class C [36].Mechanism of action of hydralazine result from relaxation of smooth muscle of arterioles, vasodilation and reducing the level of blood pressure. Since the drug has vasodilator action so the adverse effects include flushing, headache, palpitations, and with chronic use may cause rare cases of systemic lupus erythromatoses[37].

Sodium nitroprusside another intravenously used direct vasodilator used in case of serious and life threatening gestational hypertension, it cause serious side effects including thiocyanate toxicity and cardioneurogenic syncope, therefore its use limited for life threatening cases[38].

6. Renin Angiotensin Aldosterone System Drugs

The teratogenic effects of both angiotensin converting enzyme inhibitors and drugs belong to angiotensin II receptor blockers limited the use of theses agents in treatment of gestational hypertension. Food and Drug Administration classified it as class D so many studies consider the use of it is contraindicated during the pregnancy[39].

g. Management Protocol of Preeclampsia

The treatment of preeclampsia deepened on the degree of severity, if it was mild to moderate, sever or developed to eclampsia, however the only curative option for preeclampsia disorder is termination of pregnancy and deliver the baby. This premature delivery carried high risk of neonatal morbidity and mortality depended on the age of pregnancy specially if the pregnant women suffer from sever and life threatening condition[40].

A. Mild and Moderate Preeclampsia Condition

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

The bed rest and relaxation technique consider the mainstay in the management protocol in addition to therapeutic agents also play important role for the treatment. The bed rest lead to rise the blood flow to hepatic, renal, cardiovascular, and central nervous systems which contributed to stabilization of the patient. Antihypertensive drugs started when the level of diastolic blood pressure is 100mmHg or more[41].The agents recommended for this stage include:

1. Methyldopa

Started with dose equal to 750 mg per day divided to three dose/day and can be increase to reach 2000-3000mg per day according to blood pressure measurements.

2. Labetalol

The recommended daily dose is 400-800mg per day. This dose given in twice daily manner with food.

3. Nifedipine (Dihydropyridine Calicum Channel Blocker)

Used for severe cases of hypertension unresponsive to previous agents. Its use associated with vasodilation related side effects such as headache, peripheral edema, flushing and tachycardia[42].

B. Sever Preeclampsia

Sever preeclampsia cases associated with high blood pressure measurement may reach to more than 160/110mmHg, low platelet count may reach to less than 100,000/mcL and epigastric pain. If this cases accompanied with rise the reading of liver enzymes lead to sever form of preeclampsia which called HELLP syndrome, the name if this syndrome refer to the first latter of the associated symptoms : hemolysis, elevated liver enzymes, low platelet count[43].

Therapeutic agents used to managed this type of preeclampsia included the following[44]:

1. Hydralazine

Intravenously administrated hydralazine consider the most suitable choice for sever form of preeclampsia. The recommended dose governed by the mean arterial pressure (MAP) so started with 5mg (as bolus dose) IV when MAP equal or more than 125 mmHg with continuous monitoring for MAP if its level remain above 125mmHg, another bolus doses added until reach to 15mg (three bolus doses) with time interval between successive doses. When MAP level decreased less than 125mmHg the maintenance dose is 10 mg per hour as IV infusion. Due to the strong vasodilator action of hydralazine which may cause adverse effect on placental blood flow some management protocol involved the plasma volume expander agent before hydralazine treatment to maintained the plasma volume and prevent the fetal distress[45].

2. Labetalol

In sever preeclampsia management protocol intravenous labetalol classified as second line in women not adequately responsive to hydralazine, however the recommended regimen for dose rely on the mean arterial pressure so 20 mg of labetalol given IV as bolus dose when MAP above 125mmHg. If the reading of MAP not decreased the treatment guideline advised to give the patient repeated bolus doses with 10 minutes interval between the doses up to 220 mg as accumulative dose ,finally when the MAP stabilized below 125mmHg the patient received IV infusion labetalol at dose equal to 40 mg per hour which increasing up to 160 mg per hour until reach to adequate response[46].

3. Nifedipine

Nifedipine capsule (10 mg) orally is given in repeated manner every 30 to 60 minutes with continuous monitoring for diastolic blood pressure to reach the goal reading which is less than 110mmHg[47].

C. Eclampsia

The definition of eclampsia deepened on the presence of seizure in addition to other clinical finding of severe form of preclampsia[5]. The therapeutic agent used to control this disorder include the following:

1. Magnesium Sulfate

This drug consider as first line to prevent the recurrent episodes of seizure in pregnant women with eclampsia. The current guideline started with 4 gram injected intravenously over 5 to 15 minutes, then continue with 1g per hour for about 24 hours as intravenous infusion, however if the episodes of seizure reoccur additional dose equal to 2g is given as IV injection. Administration of magnesium sulfate associated with high risk of magnesium toxicity, therefore to manage this condition the patient required firstly, monitoring for any sign of toxicity like decrease the

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

depth and rate of respiration or lose the deep tendon reflexes, secondly intravenous administration of calcium gluconate over 3 minutes at dose equal to 1g(10 ml of 10 percent calcium gluconate solution)[48].

2. Diazepam

Consider as alternative choice at 10 mg dose but it usually used as adjunct therapy in convulsion condition, however many studies reported its use as mono-therapy is not effective adequately[49].

3. Phenobarbital

Anti-seizure drug related to barbiturate group could be utilized in dose equal to 2mg \Kg\day either orally or intravenously in one or twice daily dosing. The last option if the seizure not controlled by therapeutic agent ,the surgical termination of pregnancy is achieved[50].

D. Prophylactic therapy

Antiplatelet drugs, vitamins and nutrient agent could be used to during the pregnancy period for different purpose, but it benefit to reduce the occurrence or risk of preeclampsia is confliction. When 75 mg aspirin tablets used pregnant women the risk of preeclampsia, fetal death, preterm births and neonatal deaths would reduce. So many clinicians advise the pregnant women who had preeclampsia risk factors to take 75 mg of aspirin daily to get its therapeutic benefits[51].

Antioxidant vitamins like C and E vitamin could be reduced the occurrence of preeclampsia[52], however, the administration of fish oil to pregnant women has no role to reduce the gestational hypertension[53].

Drug name	FDA category	Dose	Adverse effects
Methyldopa	B	0.5 -3 mg per day given in twice daily dosing regimen	Hemolytic anemia, depression, hepatic function change.
Labetalol	C	IV route: 20-40 mg Orally : 200-1200mg given in 2-3 doses daily.	Could be limit fetal growth, with large dose cause neonatal hypoglycemia

Table 2. ***First line drugs for pregnant women with hypertension***

Drug name	FDA category	Dose	Adverse effects
Nifedipine	C	Orally:10-30 mg Long acting preperation	If short acting preperation used cause profound hypotension, could be inhibit the labor.
Verapamil	C	Orally: 80mg three time daily.	Drug–drug interaction with magnesium,bradycardia.
Clonidine	C	0.1-0.6 mg/ day (twice daily doses)	Safety similar to methyldopa but may cause lower brith weight.
Hydrochlorothiazide	B	12.5- 25 mg per day.	Rare:Electrolyte abnormalities,volume contraction.
HydralazineIV in sever cases	C	50-300 mg /day(2-4 daily doses)	Drug induced lupus ,thrombocytopenia,tachyphylaxis
Nitroprusside IV in life threatening condition	C	3mcg/Kg IV infusion over 15 hour.	Associated with cyanide and thiocyanate toxicity

Table 3. ***Second line drugs for pregnant women with hypertension***

B. Discussion

As mention previously, the reading of blood pressure is the major determinant to choice the antihypertensive agents and its route so the in cases of severe elevation or life threatening hypertension the intravenous route of rapid onset action drugs is recommended to manage the condition and prevent the complication of sever hypertension. In addition to many factors should be consider during the choice of drug to obtain the best results including ; the clinical efficacy in management of blood pressure reading, ability to prevent or minimize occurrence of hypertension complication in mother and fetus, finally the cost and availability of antihypertensive drugs.

Deepened on this factors nifedipine appear to be the best option compared with oral or IV labetalol, IV hydralazine and methyldopa. Many studies showed the administration of nifedipine produced better antihypertensive activity

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

which attributed to rapid control and reduction on blood pressure level with low dose so reduced the possibility of the side effects associated with higher doses[54], moreover, the low cost, availability, and orally administration made more palatable to patient. A randomized controlled trial performed on chronic hypertension patient conducted by Easterling et al. showed there's no statistically significant difference between antihypertensive action for the following agents (nifedipine compared with labetalol or compared with methyldopa), in other words, these agents show the same clinical action and antihypertensive activity in lowering the level of blood pressure to target measurements in patient with chronic hypertension although the nifedipine appear to has the better compliance and tolerance[55]. Nifedipine oral tablets have faster action in lowering the levels of blood pressure readings than intravenous labetalol in pregnant women suffered from severe form of preeclampsia[56]. In the same way Adebayo et al conducted study to compared the tolerance and antihypertensive activity between hydralazine and nifedipine in different route, however the finding showed that nifedipine tablets and intravenous hydralazine have same action for management blood pressure levels but in term of tolerance the oral nifedipine is better results so depended on these finding the current guideline for preeclampsia recommended the oral nifedipine as first choice in emergent condition of hypertension in pregnancy[57].

Conclusion

It is found that the administration of antihypertensive agent to women with gestational hypertension provided significant results and better prognosis for fetus and mother. The finding of several studies indicate the use of nifedipine (dihydropyridine)is more effective as antihypertensive agent when compared with other group and agents including oral or IV labetalol, methyldopa, and IV hydralazine for the management of the all form of hypertension in pregnancy involving: chronic hypertension, sever hypertension, preeclampsia, sever preeclampsia, eclampsia. Although in chronic hypertension the antihypertensive action of these agent consider to have the same effect with superiority for nifedipine in the term of tolerance, these results support the use of it as first choice in management protocol.

References

1. R.G. Sinkey, A.N. Battarbee, N.A. Bello, C.W. Ives, S. Oparil, and A.T. Tita, "Prevention, diagnosis, and management of hypertensive disorders of pregnancy: a comparison of international guidelines," Current Hypertension Reports, vol. 22, Sep. 2020.
2. C.S. Homer, M.A. Brown, G. Mangos, and G.K. Davis, "Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension," Journal of Hypertension, vol. 26, no. 2, pp. 295-302, Feb. 2008.
3. S.M. Billah, A.N. Khan, S.M. Rokonuzzaman, N.L. Huq, M.A. Khan, S.S. Priyanka, I.I. Mannan, S. Rahman, S. El Arifeen, and J. George, "Competency of health workers in detecting and managing gestational hypertension, pre-eclampsia, severe pre-eclampsia and eclampsia during antenatal check-ups in primary care health facilities in Bangladesh: a cross-sectional study," BMJ Open, vol. 11, no. 7, p. e046638, Jul. 2021.
4. L. Trogstad, P. Magnus, and C. Stoltenberg, "Pre-eclampsia: Risk factors and causal models," Best Practice & Research Clinical Obstetrics & Gynaecology, vol. 25, no. 3, pp. 329-342, Jun. 2011.
5. F. Lu, H. Gong, H. Lei, and J. Li, "Downregulation of cathepsin C alleviates endothelial cell dysfunction by suppressing p38 MAPK/NF-κB pathway in preeclampsia," Bioengineered, vol. 13, no. 2, pp. 3019-3028, Feb. 2022.
6. E. Jung, R. Romero, L. Yeo, N. Gomez-Lopez, P. Chaemsaithong, A. Jaovisidha, F. Gotsch, and O. Erez, "The etiology of preeclampsia," American Journal of Obstetrics and Gynecology, vol. 226, no. 2, pp. S844-S866, Feb. 2022.
7. J.P. Granger, B.T. Alexander, W.A. Bennett, and R.A. Khalil, "Pathophysiology of pregnancy-induced hypertension," American Journal of Hypertension, vol. 14, no. S3, pp. 178S-185S, Jun. 2001.
8. S.E. Maynard, J.Y. Min, J. Merchan, K.H. Lim, J. Li, S. Mondal, T.A. Libermann, J.P. Morgan, F.W. Sellke, I.E. Stillman, and F.H. Epstein, "Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia," The Journal of Clinical Investigation, vol. 111, no. 5, pp. 649-658, Mar. 2003.
9. N.C. Ngene and J. Moodley, "Role of angiogenic factors in the pathogenesis and management of pre-eclampsia," International Journal of Gynecology & Obstetrics, vol. 141, no. 1, pp. 5-13, Apr. 2018.
10. S.M. Hollenberg, "Vasoactive drugs in circulatory shock," American Journal of Respiratory and Critical Care Medicine, vol. 183, no. 7, pp. 847-855, Apr. 2011.
11. M. A. Brown et al., "Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice," Hypertension, vol. 72, no. 1, pp. 24-43, Jul. 2018.
12. R. Mustafa et al., "A comprehensive review of hypertension in pregnancy," J. Pregnancy, vol. 2012, Oct. 2012.
13. D. T. Gamble et al., "Hypertensive disorders of pregnancy and subsequent cardiovascular disease: current national and international guidelines and the need for future research," Front. Cardiovasc. Med., vol. 6, p. 55, May 2019.
14. A. Buchbinder et al., "Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia," Am. J. Obstet. Gynecol., vol. 186, no. 1, pp. 66-71, Jan. 2002.

15. C. J. Nobles et al., "Preconception blood pressure and its change into early pregnancy: early risk factors for preeclampsia and gestational hypertension," Hypertension, vol. 76, no. 3, pp. 922-929, Sep. 2020.
16. J. A. Hutcheon et al., "Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy," Best Pract. Res. Clin. Obstet. Gynaecol., vol. 25, no. 4, pp. 391-403, Aug. 2011.
17. M. F. Bartal et al., "Proteinuria during pregnancy: definition, pathophysiology, methodology, and clinical significance," Am. J. Obstet. Gynecol., vol. 226, no. 2, pp. S819-S834, Feb. 2022.
18. A. Tranquilli et al., "The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP," Pregnancy Hypertens., vol. 4, no. 2, pp. 97-104, Apr. 2014.
19. L. Weinstein, "Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy," Am. J. Obstet. Gynecol., vol. 142, no. 2, pp. 159-167, Jan. 1982.
20. M. Boushra et al., "High risk and low prevalence diseases: Eclampsia," Am. J. Emerg. Med., vol. 58, pp. 223-228, Aug. 2022.
21. K. P. Conrad and J. M. Davison, "The renal circulation in normal pregnancy and preeclampsia: is there a place for relaxin?," Am. J. Physiol. Renal Physiol., vol. 306, no. 10, pp. F1121-F1135, May 2014.
22. V. H. Dissanayake et al., "The urine protein heat coagulation test—a useful screening test for proteinuria in pregnancy in developing countries: a method validation study," BJOG: Int. J. Obstet. Gynaecol., vol. 111, no. 5, pp. 491-494, May 2004.
23. I. Saxena, S. Kapoor, and R. C. Gupta, "Detection of proteinuria in pregnancy: comparison of qualitative tests for proteins and dipsticks with urinary protein creatinine index," J. Clin. Diagnostic Res., vol. 7, no. 9, pp. 1846, Sep. 2013.
24. National High Blood Pressure Education Program, "Report of the national high blood pressure education program working group on high blood pressure in pregnancy," Am. J. Obstet. Gynecol., vol. 183, no. 1, pp. S1-S22, Jul. 2000.
25. T. J. Yang, R. B. Sangal, and L. W. Conlon, "Eclampsia," J. Educ. Teach. Emerg. Med., vol. 6, no. 3, p. S33, Jul. 2021.
26. J. A. Giovannitti Jr, S. M. Thoms, and J. J. Crawford, "Alpha-2 adrenergic receptor agonists: a review of current clinical applications," Anesth. Prog., vol. 62, no. 1, pp. 31-38, Mar. 2015.
27. T. Easterling et al., "Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial," Lancet, vol. 394, no. 10203, pp. 1011-1021, Sep. 2019.
28. M. L. Buchanan et al., "Clonidine pharmacokinetics in pregnancy," Drug Metab. Dispos., vol. 37, no. 4, pp. 702-705, Apr. 2009.
29. T. Podymow and P. August, "Antihypertensive drugs in pregnancy," Semin. Nephrol., vol. 31, no. 1, pp. 70-85, Jan. 2011.
30. K. Tanaka et al., "Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease," Circ. J., vol. 80, no. 10, pp. 2221-2226, Sep. 2016.
31. N. Zitoun et al., "Prospective Evaluation of Pregnancy Outcomes after Gestational Exposure to Prazosin," Br. J. Clin. Pharmacol., Jan. 2023.
32. I. Bellos et al., "Comparative efficacy and safety of oral antihypertensive agents in pregnant women with chronic hypertension: a network metaanalysis," Am. J. Obstet. Gynecol., vol. 223, no. 4, pp. 525-537, Oct. 2020.
33. D. Churchill et al., "Diuretics for preventing pre-eclampsia," Cochrane Database Syst. Rev., no. 1, Jan. 2007.
34. S. Ogura, J. Suzuki, and H. Suzuki, "Antihypertensive drug therapy for women with non-severe hypertensive disorders of pregnancy: a systematic review and meta-analysis," Hypertens. Res., vol. 42, no. 5, pp. 699-707, May 2019.
35. A. Awaludin et al., "Antihypertensive medications for severe hypertension in pregnancy: A systematic review and meta-analysis," Healthcare, vol. 10, no. 2, p. 325, Feb. 2022.
36. P. Vigil-De Gracia et al., "Severe hypertension in pregnancy: hydralazine or labetalol: a randomized clinical trial," Eur. J. Obstet. Gynecol. Reprod. Biol., vol. 128, no. 1-2, pp. 157-162, Sep. 2006.
37. L. A. Magee et al., "Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis," Bmj, vol. 327, no. 7421, p. 955, Oct. 2003.
38. J. E. Stempel et al., "Use of sodium nitroprusside in complications of gestational hypertension," Obstet. Gynecol., vol. 60, no. 4, pp. 533-538, Oct. 1982.
39. V. Regitz-Zagrosek et al., "ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)," Eur. Heart J., vol. 32, no. 24, pp. 3147-3197, Dec. 2011.
40. M. L. Costa, R. D. Cavalli, H. A. Korkes, E. V. Cunha Filho, and J. C. Peraçoli, "Diagnosis and management of preeclampsia: suggested guidance on the use of biomarkers," Revista Brasileira de Ginecologia e Obstetricia/RBGO-Gynecology and Obstetrics, vol. 44, no. 09, pp. 878-883, Apr. 2022.
41. J. N. Martin Jr, B. D. Thigpen, R. C. Moore, C. H. Rose, J. Cushman, and W. May, "Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure," Obstetrics & Gynecology, vol. 105, no. 2, pp. 246-254, Feb. 2005.
42. A. C. Levin, P. L. Doering, and R. C. Hatton, "Use of nifedipine in the hypertensive diseases of pregnancy," Annals of Pharmacotherapy, vol. 28, no. 12, pp. 1371-1378, Dec. 1994.
43. A. Rosen, M. Klein, and A. Beck, "Follow-up in HELLP syndrome," Zentralblatt fur Gynakologie, vol. 112, no. 5, pp. 273-277, Jan. 1990.
44. R. Nirupama et al., "Preeclampsia: Pathophysiology and management," Journal of Gynecology Obstetrics and Human Reproduction, vol. 50, no. 2, p. 101975, Feb. 2021.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

45. Q. A. Shahzad Qamar et al., "A review on the clinical pharmacokinetics of hydralazine," Expert Opinion on Drug Metabolism & Toxicology, vol. 18, no. 10, pp. 707-714, Oct. 2022.
46. G. M. Peres, M. Mariana, and E. Cairrão, "Pre-eclampsia and eclampsia: An update on the pharmacological treatment applied in Portugal," Journal of Cardiovascular Development and Disease, vol. 5, no. 1, p. 3, Jan. 2018.
47. S. Shekhar et al., "Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis," BJOG: An International Journal of Obstetrics & Gynaecology, vol. 123, no. 1, pp. 40-47, Jan. 2016.
48. L. Duley et al., "Magnesium sulphate and other anticonvulsants for women with pre-eclampsia," Cochrane Database of Systematic Reviews, no. 11, Nov. 2010.
49. G. M. Kassie, D. Negussie, and J. H. Ahmed, "Maternal outcomes of magnesium sulphate and diazepam use in women with severe pre-eclampsia and eclampsia in Ethiopia," Pharmacy Practice, vol. 12, no. 2, Apr. 2014.
50. A. Jagoda and S. Riggio, "Emergency department approach to managing seizures in pregnancy," Annals of Emergency Medicine, vol. 20, no. 1, pp. 80-85, Jan. 1991.
51. L. Duley et al., "Antiplatelet agents for preventing pre-eclampsia and its complications," Cochrane Database of Systematic Reviews, no. 10, Oct. 2019.
52. J. M. Roberts et al., "Vitamins C and E to prevent complications of pregnancy-associated hypertension," New England Journal of Medicine, vol. 362, no. 14, pp. 1282-1291, Apr. 2010.
53. S. F. Olsen et al., "Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: a randomised clinical trial with fish oil," European Journal of Clinical Nutrition, vol. 61, no. 8, pp. 976-985, Aug. 2007.
54. M. Zulfeen, R. Tatapudi, and R. Sowjanya, "IV labetalol and oral nifedipine in acute control of severe hypertension in pregnancy–A randomized controlled trial," European Journal of Obstetrics & Gynecology and Reproductive Biology, vol. 236, pp. 46-52, May 2019.
55. T. Easterling et al., "Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial," The Lancet, vol. 394, no. 10203, pp. 1011-1021, Sep. 2019.
56. S. Shekhar et al., "Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial," Obstetrics & Gynecology, vol. 122, no. 5, pp. 1057-1063, Nov. 2013.
57. J. A. Adebayo et al., "Efficacy of nifedipine versus hydralazine in the management of severe hypertension in pregnancy: A randomised controlled trial," Nigerian Postgraduate Medical Journal, vol. 27, no. 4, pp. 317-324, Oct. 2020.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo